Alerts, Notices, and Case Reports

Perils and Pitfalls in the Diagnosis of Cushing's Syndrome

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SPONTANEOUS CUSHING'S SYNDROME may be corticotropin-dependent due to either pituitary or ectopic hypersecretion of corticotropin, or corticotropin-independent due to primary adrenal neoplasms or nodular hyperplasia.[1] Cushing's syndrome due to pituitary or ectopic corticotropin secretion can be clinically and biochemically indistinguishable.[1,2] In recent years, advances in diagnostic imaging have led to the use of magnetic resonance imaging (MRI)[3,4] and selective venous sampling for corticotropin[5,6] as the principal tools for identifying the source of corticotropin hypersecretion. These ultrasensitive imaging techniques can be misleading, however, if their results are not interpreted with caution, as illustrated in this case report.

Report of a Case

The patient, a 68-year-old nonsmoking woman, had a four-month history of progressive weight gain, central obesity, muscle weakness, and pedal edema. She had been well before being seen, except for long-standing essential hypertension, controlled with the use of atenolol, 50 mg a day. Her initial laboratory evaluation showed hypokalemia (serum potassium level, 2.1 mmol per liter) and fasting hyperglycemia. The initial diagnosis of corticotropin-dependent Cushing's syndrome was based on the following test results: urinary 17-hydroxycorticosteroid excretion, 59.6 μmol per day (21.6 mg per day) (reference range, 5.5-22 μmol per day [2-8 mg per day]);

random serum cortisol level, 1,242 nmol per liter (45 μg per dl) (reference range, 190-690 nmol per liter [7-25 μg per dl); and plasma corticotropin level, 24.7 pmol per liter (112 pg per ml) (reference range, 2.0-11.5 pmol per liter [9-52 pg per ml]). An MRI of the pituitary gland was reported to show a 7×5-mm pituitary microadenoma. She was treated with a regimen of ketoconazole, 400 mg twice a day; spironolactone, furosemide, potassium supplements, and glyburide and referred to our institution for planned pituitary microsurgery.

On physical examination, the patient weighed 105 kg and was 157 cm tall; her blood pressure was 190/100 mm of mercury, and she had a regular heart rate of 66 beats per minute (while taking β-blockade medication). The patient had the typical appearance of Cushing's syndrome with moon facies, dorsocervical and supraclavicular fat pads, and truncal obesity. Additional findings included skin hyperpigmentation, proximal muscle weakness, and pedal edema.

The original sellar MRI was reviewed and found to be inconclusive, and a second study showed a normal pituitary gland. The patient subsequently underwent selective venous sampling from the cavernous sinuses (CS) and the inferior petrosal sinuses (IPS) to test for the central-to-peripheral (P) corticotropin gradient. This demonstrated a maximal CS:P ratio of 2.15 and an IPS:P ratio of 1.38. In view of these equivocal results, an ectopic source of corticotropin secretion was considered. Surprisingly, computed tomography (CT) of the chest revealed a solitary 4 ×4×5-cm mass in the posterior segment of the right upper lobe, with probable right hilar lymphadenopathy (Figure 1). A CT scan of the abdomen showed hyperplastic adrenal glands but otherwise no abnormalities. An overnight high-dose (8-mg) dexamethasone-suppression test was performed, and her serum cortisol level declined insignificantly from a basal value of 1,465 nmol per liter (53.1 μg per dl) to 1,335 nmol per liter (48.4 μg per dl), a result compatible with ectopic-corticotropin syndrome.

The patient underwent a total resection of the right pulmonary mass with right upper lobectomy. Intraoperatively, the mass was thought to be a probable carcinoma, and gross sectioning revealed a firm, 4.5-cm, poorly circumscribed, tan-pink mass with focal areas of hemorrhage and cavitation. The final histologic examination, however, did not show neoplasm, and staining studies showed numerous branching, beaded, gram-positive, weakly acid-fast, filamentous organisms, consistent with infection with *Nocardia* species (Figure 2). On examination of resected paratracheal and hilar lymph nodes, no neoplasm or microorganism was found. The patient had no evidence of systemic nocardiosis, as indicated by negative culture results from her blood and other sources. Following her chest surgical procedure, she had persistent hypercortisolemia, with random serum cortisol levels ranging from 1,352 to 1,876 nmol per liter

ABBREVIATIONS USED IN TEXT

CS = cavernous sinus
CT = computed tomographic
IPS = inferior petrosal sinus
MRI = magnetic resonance imaging
oCRH = ovine corticotropin-releasing hormone
P = peripheral

(49-68 µg per dl). Metyrapone tartrate, 250 mg four times a day, was added to her adrenostatic regimen. She was also given the combination of trimethoprim and sulfamethoxazole for the treatment of nocardia infection.

A renewed search for pituitary Cushing's disease was prompted by the initial surgical failure. She had another pituitary MRI, this time with the use of dynamic perfusion study with gadolinium enhancement because this was thought to improve its sensitivity for detecting small lesions. The early perfusion sequence showed a punctate focus of decreased enhancement in the inferior aspect of the gland, suggestive of a 1.7-mm pituitary microadenoma (Figure 3). This kindled further enthusiasm to search for a pituitary lesion, and another selective venous sampling for corticotropin was performed with ovine corticotropin-releasing hormone (oCRH) stimulation, giving a peak stimulated CS:P corticotropin ratio of 2.87. Despite these equivocal results, a decision was made to proceed with pituitary microsurgery, which was performed three weeks after her thoracotomy. A total hypophysectomy was performed because no focal abnormality was detected, but this failed to disclose a pituitary adenoma or to improve her postoperative plasma cortisol levels. She required levothyroxine sodium, estrogen replacement, and temporary desmopressin acetate administration for her surgically acquired hypopituitarism.

Because hypercortisolism persisted after the hypophysectomy, an ectopic source of corticotropin production was evidently present in this patient. An MRI of the chest and upper abdomen was repeated with dynamic perfusion study to increase its sensitivity for tumor localization. The chest study showed normal findings, whereas the rapid-sequence MRI of the upper abdomen demonstrated a 1-cm area of high signal intensity in the midbody of the pancreas. The lesion was reported to be vascular due to gadolinium enhancement and considered compatible with a carcinoid or islet cell tumor. This was felt to be the source of corticotropin production, and thus resection of the pancreatic mass was planned, with simultaneous bilateral adrenalectomy if the probability of cure from pancreatic resection was thought to be low. The patient underwent her third surgical procedure two weeks after the hypophysectomy and just over a month from her first operation in the pursuit of the cause of her Cushing's syndrome. Intraoperatively, a cyst was found within her pancreas, and excisional biopsy with frozen section failed to show any evidence of tumor; thus, bilateral adrenalectomy was done. Her postoperative course was

Figure 1.—An axial computed tomographic scan through the lung photographed on lung windows demonstrates a mass lesion emanating from the right paraspinus area (arrows). Resection revealed a nocardial abscess.

complicated by pancreatitis with pancreatic pseudocyst formation, which resolved with percutaneous drainage.

After the bilateral adrenalectomy, the patient's serum cortisol levels fell to 55 to 83 nmol per liter (2-3 µg per dl) whereas her plasma corticotropin levels remained high at 11.0 to 27.5 pmol per liter (50-125 pg per ml). Further pursuit of the source of ectopic corticotropin secretion using indium In 111 pentetreotide whole-body scintigraphy again failed to elicit the source. Nevertheless, the hypokalemia and hyperglycemia resolved, and the patient had improvement in hypertension control. She was able to discontinue her adrenostatic drugs, although requiring a regimen of prednisone, 30 mg a day (with a gradual taper to a replacement dosage), and fludrocortisone acetate, 0.1 mg a day.
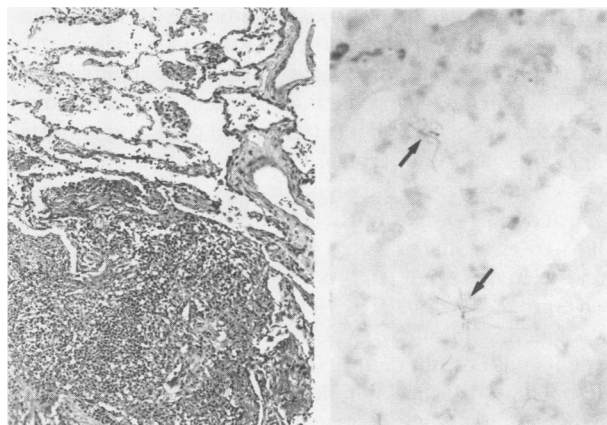

Figure 2.—Photomicrographs of the resected pulmonary lesion: Left, A specimen of lung tissue is shown, with the lower portion demonstrating acute inflammation and necrosis (hematoxylin and eosin stain, original magnification ×20). Right, Arrows show examples of the slender, branching, filamentous forms of Nocardia species (Gram's stain, original magnification ×200).
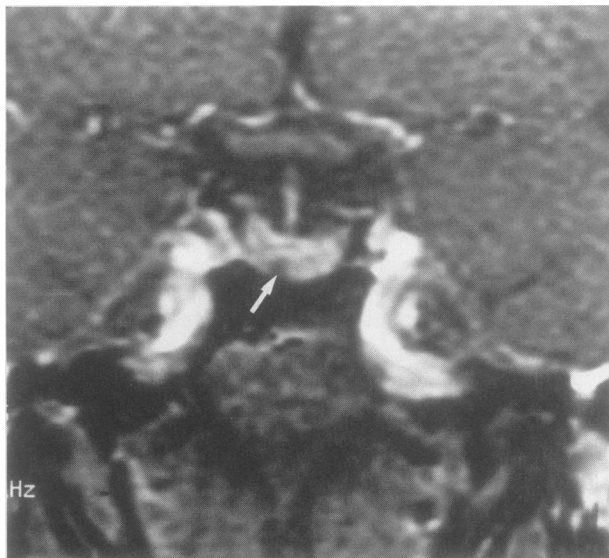
Figure 3.—Coronal dynamic pituitary magnetic resonance scan: A T1-weighted coronal scan obtained during the infusion of gadolinium pentetate demonstrates a focal hypointense lesion (arrow) at the floor of the sellar just to the right of the midline.

Discussion

The occult ectopic-corticotropin syndrome represents an important form of spontaneous hypercortisolism that is often clinically indistinguishable from pituitary-dependent Cushing's disease.[1,2] This case exemplifies the perils and pitfalls of current imaging techniques in the differential diagnosis of corticotropin-dependent hypercortisolism. Despite the greater reliance on these sophisticated tools, certain clinical or biochemical features are helpful clues to differentiate between pituitary-dependent and ectopic Cushing's syndrome.[7-9] As illustrated by this case, features such as a relatively rapid onset of symptoms, substantial muscle weakness, skin hyperpigmentation, edema, hypertension, and spontaneous hypokalemia are all more commonly associated with ectopic Cushing's syndrome. In reviewing all reported cases of bronchial carcinoid with ectopic corticotropin production, Leinung and co-workers[8] found that 69 of 74 patients (93%) had clinical manifestations consistent with typical Cushing's disease; however, hypokalemia (serum potassium level, <3.3 mmol per liter) occurred in 41 of 59 of patients (69%) as compared to less than 10% in patients with a pituitary source from another series.[9] In a review of 16 patients with ectopic corticotropin secretion, Howlett and colleagues found hypokalemia in all patients, including a subgroup of 10 patients with occult tumors (although 2 patients were taking potassium-losing diuretics).[9] Proximal myopathy was also noted in all their patients with occult tumors.

Hormonal studies often fail to differentiate clearly between the pituitary and ectopic sources of corticotropin secretion because of considerable overlap of test results, including pharmacologic testing such as the dexamethasone-suppression test, the metyrapone stimulation test, and the oCRH stimulation test.[2,7] In our patient, howev-

er, results from the pharmacologic study were consistent with the diagnosis of ectopic corticotropin secretion, as her cortisol level remained nonsuppressible after high doses of dexamethasone were administered.

Many investigators have relied directly on MRI of the pituitary gland or selective venous sampling for corticotropin (or both) in the diagnostic evaluation of corticotropin-dependent hypercortisolism.[3-6] The accuracy of pituitary imaging to distinguish Cushing's disease from ectopic corticotropin secretion is limited by the relatively high incidence of incidental pituitary microadenomas in the normal population, as reported in as many as 20% of adults.[10,11] This is further confounded by the fact that pituitary corticotropic adenomas are often less than 5 mm in size, and as many as 50% may be undetectable on MRI.[7] Although the presence of a pituitary lesion in our patient was not convincingly demonstrated by the conventional sellar MRI, a subsequent dynamic-flow study with gadolinium contrast, a technique that enhances the detection of pituitary microadenomas by assessing the differential time lag in contrast enhancement between tumoral and normal pituitary tissue,[12] showed unequivocally the presence of a tiny intrapituitary lesion. Transsphenoidal surgical procedure, however, neither revealed a corticotropic adenoma nor resulted in a cure for our patient, indicating that dynamic-flow MRI may be subject to artifacts, with compromised specificity. Unexpectedly, the result of dynamic-flow MRI of the pancreas was again erroneous, leading to an inappropriate pancreatic operation.

Selective venous sampling for corticotropin from bilateral IPS has been widely regarded as the most accurate method for differentiating between pituitary-dependent Cushing's disease and ectopic Cushing's syndrome.[2,5-7] Doppman and associates performed selective venous sampling for corticotropin from bilateral IPS in a large series of patients from the National Institutes of Health and found no false-positive results in identifying Cushing's disease in basal specimens when the IPS:P corticotropin ratio was 2 or higher. After oCRH stimulation, they found that a peak IPS:P corticotropin ratio of 3 or higher identified all patients with Cushing's disease with no false-positive results, indicating 100% sensitivity and specificity.[6] Superselective venous sampling from bilateral CS, developed by Teramoto and colleagues, has been reliable in diagnosing Cushing's disease, if the CS:P corticotropin gradient is greater than 10, without the need for oCRH stimulation.[13] Because of poor availability of oCRH until recently, superselective venous sampling from bilateral CS is being used in our center because this has shown improved diagnostic accuracy. Patients must have hypercortisolemia at the time of sampling, however, for the study to be valid because false-positive results have been reported in patients with ectopic corticotropin secretion who manifest periodic hormonogenesis.[14]

Superselective venous sampling for corticotropin did not resolve the diagnostic dilemma in this case because the results were equivocal. There have been substantial

differences in the central-to-peripheral corticotropin ratios used by different investigators to distinguish pituitary from ectopic sources of corticotropin. Following the more recent National Institutes of Health data,[15] which apply similar cutoff values for corticotropin sampling from either IPS or CS, the initial unstimulated CS:P corticotropin ratio (2.15) could be considered positive for a pituitary source of corticotropin secretion in this patient. Conversely, this gradient is grossly inadequate for locating a pituitary source of corticotropin secretion if the criteria from Teramoto and co-workers are followed (discussed earlier).[13] The interpretation of corticotropin ratios after oCRH stimulation can likewise be difficult: a similar IPS:P corticotropin ratio of greater than 2 is used by Findling and associates for sampling before or after oCRH stimulation,[16] whereas other investigators use a higher cutoff for ratios after oCRH stimulation.[6,15,17] This case illustrates the subtleties involved in interpreting selective venous sampling results, especially when borderline values occur. The different criteria used to differentiate between pituitary and ectopic corticotropin production are likely due to several factors such as sampling techniques and accuracy, methods of corticotropin measurement, and patient variations. Because this is a highly technical procedure, the use of selective venous sampling is best confined to a few specialized centers that have sufficient experience to provide their own diagnostic criteria.

Because most lesions from occult ectopic-corticotropin syndrome are in the thorax, CT or MRI of the chest is usually performed as part of the diagnostic evaluation.[7-9] Unexpectedly, the lesion detected on chest CT scan represented a false-positive finding in this case, proving histologically to be pulmonary nocardiosis. This illustrates that the cause of pulmonary mass lesions in patients with Cushing's syndrome may not be clinically evident. Biopsy of all such lesions is indicated because a tissue diagnosis is essential to guide management. In a review of 23 patients with endogenous Cushing's syndrome (most of whom had ectopic-corticotropin syndrome) and opportunistic infections, nocardiosis, as occurred in our patient, along with cryptococcosis, aspergillosis, and *Pneumocystis carinii* pneumonia, constituted the predominant conditions.[18] Manifestations of infections in such patients are often masked by the hypercortisolism, as was the case in our patient.

Because many neuroendocrine tumors may express somatostatin receptors, radiolabeled somatostatin analogue scintigraphy has been introduced for tumor localization. This has been promoted as a new investigative tool in patients with suspected ectopic-corticotropin syndrome because eutopic corticotropic pituitary adenomas do not usually express somatostatin receptors.[19] In vivo scintigraphy with In 111pentetreotide, however, failed to show any abnormal uptake in our patient. Although lacking published data, our institutional experience thus far has indicated disappointing results in the use of pentetreotide scan to locate "occult" ectopic-corticotropin tumors.

In cases wherein the source of corticotropin-dependent Cushing's syndrome cannot be identified, bilateral adrenalectomy should be considered early to initiate prompt and effective control of hypercortisolism. Because of recent advances in laparoscopic surgery, patients can now undergo bilateral adrenalectomy with minimal morbidity and a shortened hospital stay.[20] Conversely, medical adrenal blockade with ketoconazole, metyrapone, or aminoglutethimide commonly fails to achieve satisfactory control of hypercortisolism.[21,22] Our patient showed remarkable improvement in her metabolic status after bilateral adrenalectomy, with the successful withdrawal of antiadrenal drugs, hypoglycemic agents, diuretics, and potassium supplements.

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